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How liver 'talks' to muscle: A well-timed, coordinated conversation

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A major collaborative research effort involving scientists at Harvard School of Public Health (HSPH), Brigham and Women's Hospital (BWH) and Harvard University have uncovered a novel signal mechanism that controls how fat storage in the liver can communicate with fat burning in skeletal muscle.

Especially striking is that 1) this 'conversation' involves one nuclear receptor-controlling gene expression in the liver influencing another nuclear receptor in muscle, 2) this circuit is influenced by day-night cycles, and 3) the research team identified a specific circulating lipid molecule that plays the role of messenger between liver and muscle.

The study will appear in the October 24, 2013 issue of *Nature*.

Maintaining the overall balance of energy involves the ability to use fatty acids to make lipids, a process known as de novo lipogenesis that occurs in the liver. Fatty acids are also burned to generate energy, as occurs in skeletal muscle. Given differences in the need for an organism to burn fatty acids while awake versus asleep, prior work has suggested that lipogenesis, and the genes involved in these pathways, vary in circadian (day-night) patterns.

Programs for energy use and storage are regulated by nuclear receptors—transcription factors that control entire programs of genes. PPAR delta regulates lipogenesis and PPAR alpha governs fatty acid oxidation. Disordered lipogenesis and fatty acid oxidation are important

contributors to obesity-associated problems like fatty liver and diabetes.

In the study, researchers demonstrate that when the liver makes fat through lipogenesis, a signal is sent to skeletal muscle cells to burn fat through fatty acid oxidation. The fat-making process in the liver is controlled by PPAR delta, while the fat-burning process in muscle is controlled by PPAR alpha. Using a process of isolating lipid molecules appearing in plasma, the researchers uncovered a specific lipid molecule, namely a phospholipid that is released by the liver into the blood stream under the control of PPAR delta and serves as the signal to PPAR alpha in skeletal muscle.

Mice lacking PPAR delta in the liver lost production of this molecule while mice lacking PPAR alpha no longer responded to this signal. This pathway between liver and muscle also exhibited a circadian rhythm. Moreover, high-fat feeding altered these processes, consistent with other data implicating obesity effects on normal day-night cycles.

"This finding uncovers a joint effort of the liver and muscle to maintain balanced fat production and burning, a biological process tailored to match the body's energy demands and maximize fuel-burning efficiencies during the day versus night," said Chih-Hao Lee, PhD, HSPH associate professor of Genetics and Complex Diseases, corresponding senior author.

"It is increasingly evident that metabolic responses and diseases influenced by metabolic abnormalities, involve coordinated changes in organs like the liver and muscle," said Jorge Plutzky, MD, director of the BWH Vascular Disease Prevention Program, senior co-author. "By identifying a liver-to-muscle circuit involving fat storage and fatty acid oxidation, and a naturally occurring candidate molecule involved in directing these effects, this study highlights the nature of such integrated responses, and the evolving power of combining traditional experimental

models in cells and pre-clinical models with profiling approaches like lipidomics."

The researchers are now studying how this phospholipid is carried in the circulatory system and delivered to muscle. They hope the work generates greater understanding of normal metabolism in liver and muscle and provides new therapeutic opportunities to treat fatty liver, obesity and diabetes.

More information: A diurnal serum lipid integrates hepatic lipogenesis and peripheral fatty acid use, DOI: 10.1038/nature12710

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